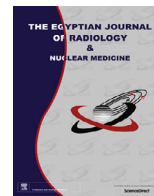




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## Original Article

# Role of quantitative chemical shift magnetic resonance imaging and chemical shift subtraction technique in discriminating adenomatous from non adenomatous adrenal solid lesions

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## ABSTRACT

**Purpose:** To evaluate role of quantitative assessment of chemical shift MR imaging and chemical shift subtraction technique in differentiating adenomatous from non-adenomatous adrenal lesions with comparison of accuracy level of each technique.

**Materials and methods:** A prospective study was carried out from 4-2014 to 5-2016 using 1.5T MRI. In-phase/opposed phase MRI sequences were applied for 52 patients having 58 adrenal lesions, 18 were hyper functioning and 40 were non-functioning. Lesions signal changes between in- and opposed phase sequences and post processing was done to calculate different quantitative chemical shift parameters using spleen, paraspinal muscle, and liver as a reference tissues. Additionally subtraction chemical shift MR technique on selected 16 cases was applied.

**Results:** Signal intensity index and the two formulas of adrenal to spleen ratio were more accurate than other quantitative chemical shift MRI parameters in discrimination between adenomatous and nonadenomatous adrenal lesions with selected cutoff value 23.4% for the signal intensity index, 0.72 and –27.82% for adrenal to spleen ratio% using the old and new formulas respectively. Chemical shift subtraction technique expressed significant difference between adenomas and non-adenomatous adrenal lesions where adenomas had ratio of 108.87 or more, and the non-adenomatous lesions had ratio of 47.74 or less with selected cutoff value 173.0475.

**Conclusion:** The signal intensity index and adrenal to spleen ratio are the most reliable quantitative chemical shift MRI methods in differentiation of adrenal adenomas from other non-adenomatous adrenal solid lesions. Chemical shift subtraction MRI is a recent technique that gives highly confident discrimination between two categories of pathology without using of any reference organ.

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## 1. Introduction

In spite of its small size, the adrenal gland included a wide range of diseases, up to 9% of them detected in autopsy. Disease spectrum includes hormonal dysfunction abnormalities, benign and malignant neoplastic lesions (whether primary or secondary) as well as infiltrative disease [1].

Recent revolutions in the field of laboratory investigations and radiological imaging much facilitated the diagnosis of such disease varieties [2,3].

Most of incidentalomas (incidentally discovered adrenal lesions), are non-functioning and being benign while 10% are functional and less than 5% being malignant. The difficulty that most of incidentalomas, whatever their nature, seem to be of rather similar pattern in cross sectional imaging [4–6].

Incidence of adrenal adenomas increased in correlation with patient's age reaching 6% of over sixty patients. Up to 50% of detected adrenal masses in patient with a known primary extra-adrenal malignancy considered metastatic. The dilemma being in differentiating benign adenoma from metastasis as the later will

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downgrade the staging and prognosis of their primary malignancy, hence appropriate characterization is mandatory [7].

MRI applications in adrenal imaging is of great value due to high capability for tissue characterization, limiting the differential diagnosis or reaching an accurate final diagnosis [8].

The chemical shift is being the most sensitive technique used for detection of lipid in adrenal lesion even with very minute quantities and depending on this fact, chemical shift MRI technique is sensitive for diagnosing adrenal adenoma; even it could replace unenhanced CT with avoidance of hazards of radiation exposure. High sensitivity and specificity based on differentiating adrenal adenoma with abundant intra-cytoplasmic fat content from adrenal metastasis which don't show any signal changes between in phase to out phase imaging [9].

Adrenal masses are more accurately characterized by quantitative rather than qualitative method of chemical shift MR [10,11]. Multiple quantitative chemical shift imaging studies have been reported trying to reach accurate diagnosis of adrenal masses using different methodology with variable magnetic field strengths, gradient strengths, and different Ref. tissues in the formulas used for quantitative calculation of signal changes including the spleen [12–14], the liver [15–18] and paraspinal muscles [17,19].

In current study, we aimed to evaluate role of quantitative assessment of chemical shift MR imaging and chemical shift subtraction technique in differentiating adenomatous from non-adenomatous adrenal lesions with comparison of accuracy level of each technique.

## 2. Materials and methods

Current prospective study was carried out between 4 and 2014 and 5–2016, included 52 patients presented with 58 solid adrenal lesions that were evaluated using MRI 1.5 T. Included patients having previously diagnosed adrenal lesion based mainly upon previous CT studies. Patient's age range was from 21 to 77 years (mean 44.77 years), equal male to female ratio and right to left side ratio was 3:2.8. The study was approved by the faculty ethics committee and informed consent was taken from each patient.

Exclusion criteria included lesions having predominate extra-cellular fat contents as myelolipoma, cases of adrenal hyperplasia and hemorrhage (in newborns or due to trauma), purely cystic lesions (simple cyst or pseudo-cyst) and adrenal lymphatic malformation. Also solid lesions with longest diameter less than 1 cm were excluded because of the technical difficulty of setting the region of interest over them without avoidance of partial volume artifacts production at the lesion edges.

Histopathological date (whether open or laparoscopic adrenalectomy) used to confirm the diagnosis of all adrenal lesions. Metastatic tumors were assessed by percutaneous needle biopsy in 4 cases presented with 6 adrenal masses.

MRI examinations was done using 1.5-T superconductive unit (1.5 T Philips Achieva Gyroscan, Best, Netherlands) for 52 cases, using phased-array body coil. Lesion localization done first using routine sequences followed with chemical shift sequence at the adrenal lesion level using in-phase/opposed-phase sequence.

Chemical shift sequence is a refocused dual gradient echo sequence using the following parameters (fast field echo (FFE), TR 130 ms, double TEs of 4.6 and 2.3 ms) used for out-of-phase and in-phase images respectively, (flip angle 80°, slice thickness 3 mm, intersection gap 0.3 mm, FOV390/1.4 and 192 × 256 matrix size, number of echoes = 2).

Spleen, liver, and para-spinal muscles were imaged at same slice as the adrenal lesion whenever possible. Patients held their breath after full expiration with each breath-hold lasted about 16–20 s and the total imaging time was less than 2 min.

Last group of cases (17 cases) presented throughout the past year of the study (distributed as 11 adenomas, 4 pheochromocytomas, 1 metastasis and 1 carcinoma) subjected to additional chemical shift MRI sequence which performed using a double-echo fast low-angle shot (FLASH) sequence obtained at the level of the adrenal lesion using the following parameters (single 19 s breath hold, TR 133 ms, doublets of 2.2 and 4.4 ms for opposed-phase and in-phase respectively, flip angle 75°, 6-mm slice thickness, 192 × 256 matrix, field of view of 300–350 mm, intersection gap 0.6 mm, and one signal acquisition). Subtraction images obtained by subtracting opposed phase images from in-phase images using the system's commercially available software.

Post processing with Philips-EWS workstation where signal intensities of adrenal lesions and their reference tissues (spleen, liver and ipsilateral para-spinal muscles) measured using generated circular regions of interest (ROI) covering widest dimension of the adrenal lesion, avoid partial volume artifact at the lesion edge, avoiding necrotic, cystic, hemorrhagic and calcific portions whenever possible.

Regarding the reference tissues, ROI must be as large as possible to be representative of the particular tissue excluding intrahepatic blood vessels (best at posterior segment of right lobe) and also avoid putting the ROI on obvious fat striations in the paraspinal muscle and other reference organs whenever possible. If splenic tissue was not present on the same slice, the closest available slice was used.

Measurements were repeated at same axial images and same adrenal position and selected reference tissues in both in-phase and out of phase corresponding images with similar surface area of ROI in similar location in both sequences. In post processing, subtraction of out of phase from in-phase chemical shift images was done then the subtracted images were quantitatively calculated.

Four quantitative chemical shift parameters of signal intensity (SI) changes between the out of-phase and the in-phase images were calculated as follows:

- **Signal intensity index (SII):** calculated used this formula  $[(SI \text{ on in-phase imaging} - SI \text{ on opposed-phase imaging}) / (SI \text{ on in-phase imaging})] \times 100\%$ .
- **Adrenal to spleen ratio:** calculated using new formula as  $\{[(adrenal \text{ SI on opposed-phase imaging} / spleen \text{ SI on opposed-phase imaging}) / (adrenal \text{ SI on in-phase imaging} / spleen \text{ SI on in-phase imaging})] - 1\} \times 100\%$ .
- **Adrenal to liver ratio:** calculated as  $\{[(adrenal \text{ SI on opposed-phase imaging} / liver \text{ SI on opposed-phase imaging}) / (adrenal \text{ SI on in-phase imaging} / liver \text{ SI on in-phase imaging})] - 1\} \times 100\%$ .
- **Adrenal to muscle ratio:** calculated as  $\{[(adrenal \text{ SI on opposed-phase imaging} / muscle \text{ SI on opposed-phase imaging}) / (adrenal \text{ SI on in-phase imaging} / muscle \text{ SI on in-phase imaging})] - 1\} \times 100\%$ .

Previously, adrenal to spleen ratio was calculated as  $\{[(adrenal \text{ SI on opposed-phase imaging} / spleen \text{ SI on opposed-phase imaging}) / (adrenal \text{ SI on in-phase imaging} / spleen \text{ SI on in-phase imaging})] - 1\}$  and that was included in current study to distinguish the most sensitive and specific ratio for diagnosis of adrenal adenoma.

## 3. Radiologist's observations and statistical analysis

Images of different adrenal lesions were presented for two experienced radiologists of abdominal MRI interpretation (A.R. and A.H.) who had 6 and 12 years experience in the field of genitourinary imaging respectively. Both of them were asked to classify lesions whether adenomatous or non-adenomatous depending on

signal drop in opposed phase images then to calculate the mentioned four chemical shift quantitative parameters (including adrenal-to-spleen ratio using the old formula as mentioned before). Comparing the five parameters using independent samples *t*-test, scatter plotting and ROC curves using IBM SPSS version 20 software computed program.

#### 4. Results

The quantitative chemical shift parameters, namely signal intensity index, adrenal to spleen, adrenal to liver, and adrenal to muscle ratios were used to differentiate both types of adrenal lesions to verify statistically significant difference. The mean values of both types were tested using Mann-Whitney test and analysis of the results was presented in Table 1.

Current results showed mean  $\pm$  SD diameters of adenomatous adrenal lesions were  $2.4 \pm 0.8$  (ranged from 1.4 to 4.3 cm) and that for non-adenomatous lesions were  $7.3 \pm 3.5$  (ranged from 2.8 to 14.5 cm).

Also mean and standard deviation of signal intensities for adrenal adenomas was  $54.52 \pm 14.16$  (range, 30.50–71.20), and  $6.65 \pm 5.56$  (range, 0.40–16.30) for non-adenomatous adrenal lesions. Using old formula of adrenal to spleen ration%, the mean and standard deviation of signal intensities for adrenal adenomas was  $0.48 \pm 0.15$  (range, 0.30–0.69), while was  $0.95 \pm 0.08$  (range, 0.75–1.06) for non-adenomatous adrenal lesions. On the other hand, using the new formula of adrenal to spleen ration%, the mean

$-52.38 \pm 14.54$  (range,  $-70.30$  to  $-30.68$ ), while was  $-4.52 \pm 8.33$  (range,  $-24.95$  to  $6.00$ ) for non-adenomatous lesions.

Using the scatterplots to compare between the chemical shift parameter values to discriminate adenomatous from non-adenomatous adrenal lesions, we found that there was no overlap signal intensity difference resulted from the chemical shift equations between both adrenal adenomas and non-adenomatous lesions using the first three mentioned chemical shift parameters and this was demonstrated in Fig. 1(a–c) that showed scatterplot of the quantitative data of both adrenal adenomatous and non-adenomatous using the adrenal signal intensity % (Fig. 1a), old formula of adrenal to spleen ratio% (Fig. 1b), and new formula of adrenal to spleen ratio% (Fig. 1c), chemical shift parameters respectively.

Results of adrenal to liver ratio % showed that the mean and standard deviation of signal intensity difference resulted from the chemical shift equation for adenomas was with  $-45.51 \pm 19.03$  (range,  $-69.43$  to  $-4.65$ ), while it was  $7.24 \pm 14.62$  (range,  $-8.40$  to  $46.37$ ) for non-adenomatous adrenal lesions. Mean and standard deviation of signal intensity difference resulted from the chemical shift equation for adrenal to muscle ratio % for adenomas was with  $-41.41 \pm 22.17$  (range,  $-69.85$  to  $-4.50$ ), while was  $6.46 \pm 12.46$  (range,  $-9.31$  to  $35.61$ ) for non-adenomatous adrenal lesions.

Small overlap in signal intensity difference resulted from the chemical shift equations was found when using the adrenal to liver ratio % and adrenal to muscle ratio %, seen in Fig. 1(d–f) which showed scatterplot of the quantitative data of both adrenal adeno-

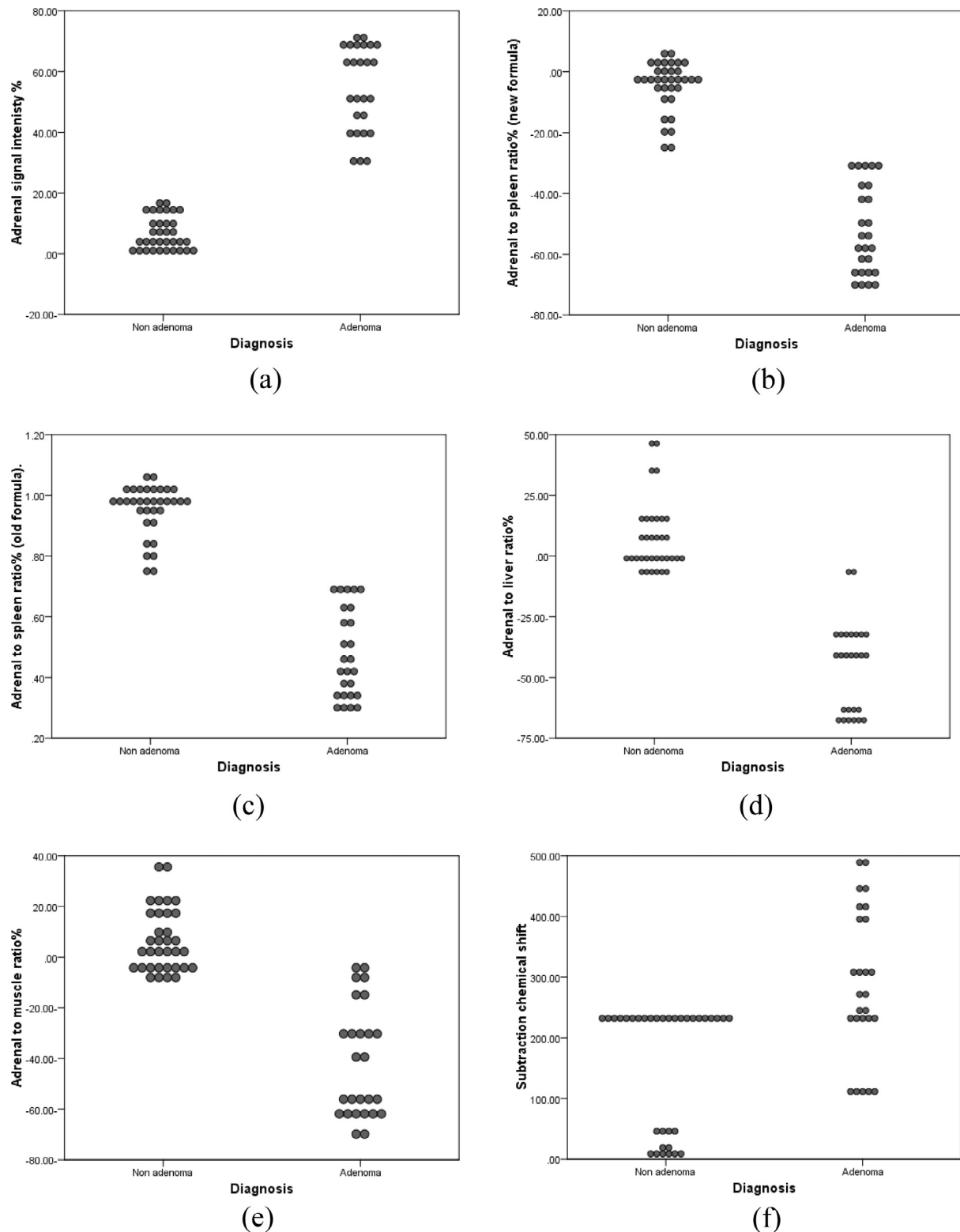
**Table 1**

Comparison of chemical shift quantitative parameters in differentiation of adenomatous and non adenomatous adrenal lesions with the mean, St. deviation, range of each parameter and its significance.

| Chemical shift parameter               |         | Diagnosis   |         | Total  | P       |
|--|---------|-------------|---------|--------|---------|
|  |         | Non adenoma | Adenoma |        |         |
| Adrenal signal intensity%              | Minimum | 0.40        | 30.50   | 0.40   | <0.001* |
|  | Maximum | 16.30       | 71.20   | 71.20  |         |
|  | Mean    | 6.65        | 54.52   | 27.39  |         |
|  | SD      | 5.56        | 14.16   | 25.97  |         |
|  | Median  | 5.00        | 57.15   | 15.05  |         |
| Adrenal to spleen ratio% (old formula) | Minimum | 0.75        | 0.30    | 0.30   | <0.001* |
|  | Maximum | 1.06        | 0.69    | 1.06   |         |
|  | Mean    | 0.95        | 0.48    | 0.75   |         |
|  | SD      | 0.08        | 0.15    | 0.26   |         |
|  | Median  | 0.98        | 0.44    | 0.82   |         |
| Adrenal to spleen ratio (new formula)  | Minimum | -24.95      | -70.30  | -70.30 | <0.001* |
|  | Maximum | 6.00        | -30.68  | 6.00   |         |
|  | Mean    | -4.52       | -52.38  | -25.26 |         |
|  | SD      | 8.33        | 14.54   | 26.46  |         |
|  | Median  | -2.00       | -55.98  | -17.71 |         |
| Adrenal to liver ratio%                | Minimum | -8.40       | -69.43  | -69.43 | <0.001* |
|  | Maximum | 46.37       | -4.65   | 46.37  |         |
|  | Mean    | 7.24        | -45.51  | -15.62 |         |
|  | SD      | 14.62       | 19.03   | 31.11  |         |
|  | Median  | -0.55       | -41.13  | -5.08  |         |
| Adrenal to muscle ratio%               | Minimum | -9.31       | -69.85  | -69.85 | <0.001* |
|  | Maximum | 35.61       | -4.50   | 35.61  |         |
|  | Mean    | 6.46        | -41.41  | -14.28 |         |
|  | SD      | 12.46       | 22.17   | 29.45  |         |
|  | Median  | 2.50        | -47.38  | -5.21  |         |
| Chemical shift subtraction MR images   | Minimum | 4.17        | 108.87  | 4.17   | <0.001* |
|  | Maximum | 232.00      | 488.98  | 488.98 |         |
|  | Mean    | 157.86      | 287.67  | 214.11 |         |
|  | SD      | 102.45      | 120.48  | 127.39 |         |
|  | Median  | 232.00      | 271.60  | 232.00 |         |

P: Mann-Whitney test.

\* P < 0.01 (significant).



**Fig. 1.** Scatterplots show differences in all calculated quantitative chemical shift parameters used to differentiate adenomas from non-adenomatous adrenal lesions. No significant overlap seen in the three parameters adrenal signal intensity, adrenal to spleen ratio using the new and old formula respectively (a–c), considerable overlap is seen in adrenal to liver ratio (d), and adrenal to muscle ratio (e) and subtraction chemical shift technique (f).

matous and non-adenomatous using the adrenal to liver ratio % (Fig. 1d) and adrenal to muscle ratio % (Fig. 1e).

The result of subtraction chemical shift measurements showed that the mean and standard deviation signal intensities of chemical shift subtraction MR images for adenomatous adrenal lesions was

with  $287.67 \pm 120.48$  (range, 108.87–488.98) while was  $157.86 \pm 102.45$  (range, 4.17–232) for non-adenomatous adrenal lesions.

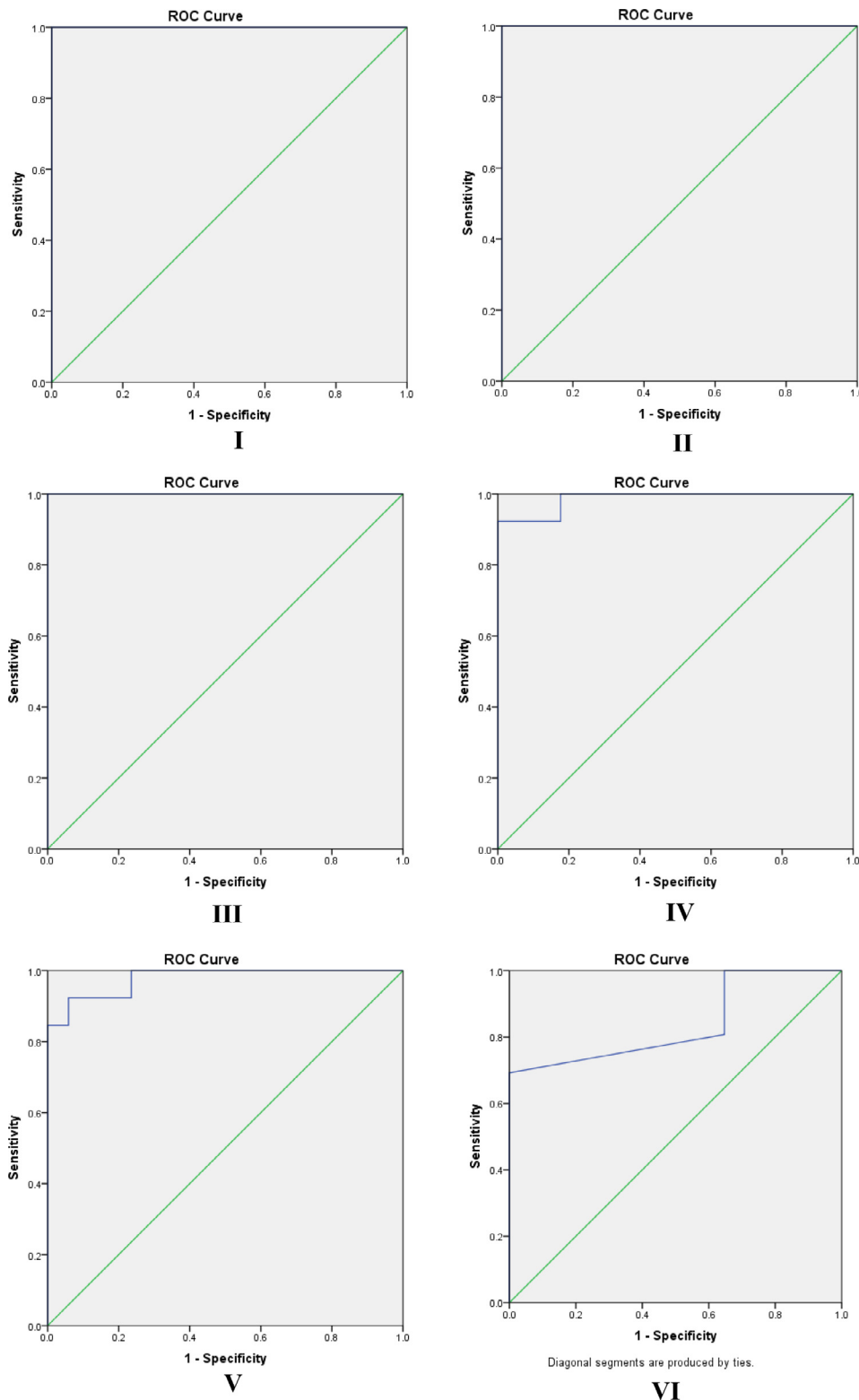
There was significant overlap in signal intensity between adrenal adenomas and non-adenomatous lesions seen in Fig. 1(f) which

showed scatterplot of the quantitative data of both adrenal adenomatous and non-adenomatous chemical shift subtraction MR images.

All measured quantitative chemical shift parameters and chemical shift subtraction technique showed significant statistical

difference between adenomas and non-adenomas lesions with ( $p < 0.001$ ).

The ROC curves of the all the calculated quantitative chemical shift parameters used for differentiation were represented in Fig. 2. Az values of the mean area under curve (AUC) and standard



**Fig. 2.** Graph shows receiver operating characteristic curves (ROC) using the all calculated chemical shift parameters; signal intensity index (I) and adrenal to spleen ratio new formula (II), adrenal to spleen ratio old formula (III), adrenal to liver ratio (IV), adrenal to liver ratio (V) and subtraction chemical shift technique (VI) to differentiate adenomatous and non-adenomatous adrenal solid lesions.

**Table 2**

Mean area under the curve (Az) values with standard error and the statistic significance of all quantitative chemical shift parameters for differentiation of adrenal adenomas from other non adenomatous adrenal lesions with coordinates of each curve.

| Chemical shift parameter               | Area (Az) | Std. error <sup>a</sup> | Asymptotic sig <sup>b</sup> | Asymptotic 95% confidence interval |             | Coordinates of the curve                     |             |               |
|--|-----------|-------------------------|-----------------------------|------------------------------------|-------------|--|-------------|---------------|
|  |           |                         |                             | Lower bound                        | Upper bound | Cut off value                                | Sensitivity | 1-Specificity |
| Signal intensity index %               | 1.000     | 0.000                   | 0.000                       | 1.000                              | 1.000       | Positive if greater than or equal to 23.40%  | 1.00        | 0.00          |
| Adrenal to spleen ratio% (old formula) | 1.000     | 0.000                   | 0.000                       | 1.000                              | 1.000       | Positive if lesser than or equal to 0.72     | 1.00        | 0.00          |
| Adrenal to spleen ratio% (new formula) | 1.000     | .000                    | .000                        | 1.000                              | 1.000       | Positive if lesser than or equal to –27.82   | 1.00        | 0.00          |
| Adrenal to liver ratio %               | 0.986     | 0.011                   | 0.000                       | 0.965                              | 1.000       | Positive if lesser than or equal to –20.0050 | 0.923       | 0.00          |
| Adrenal to muscle ratio %              | 0.977     | 0.015                   | 0.000                       | 0.948                              | 1.000       | Positive if lesser than or equal to –6.0500  | 0.923       | 0.118         |
| Subtraction chemical shift             | 0.838     | 0.057                   | 0.000                       | 0.727                              | 0.949       | Positive if lesser than or equal to 173.0475 | 0.808       | 0.647         |

<sup>a</sup> Under the nonparametric assumption.

<sup>b</sup> Null hypothesis: true area = 0.5.

errors as well as their statistical significance for these parameters are represented in Table 2.

Az value for signal intensity index and adrenal to spleen ratio with its old and recent formulae were the highest values among all applied parameters with the Az value = 1.000 for each of them and the statistical significance ( $p = 0.000$ ) was equal for all chemical shift parameters as well as for the subtraction chemical shift technique.

Cases distribution as follow: 24 adenoma cases whether functioning (Fig. 3) or non-functioning (Fig. 7), 16 pheochromocytoma (Fig. 9), 8 adreno-cortical carcinoma (Fig. 5 with IVC thrombosis and Fig. 6), 6 metastatic (Fig. 8), 2 ganglio-neuroma (Fig. 4) and finally two sarcomas.

All the adenomas had signal intensity indexes of 30.5% or more, whereas all the non-adenomatous adrenal lesions had signal intensity indexes of 16.3% or less. If the value for the signal intensity index was taken from this range (16.3–30.50%), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was 100%, and cutoff value calculated from the ROC curve indicate that any adrenal lesion with signal intensity index equal to or more than 23.4% indicate adenoma.

Using old formula of adrenal to spleen ratio, all adrenal adenomas had ratio of 0.69 or less, whereas all the non-adenomatous lesions ratio of 0.72 or more. If this range was taken (0.69–0.72), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was 100%, and the cutoff value calculated from ROC curve indicate that any adrenal lesion with adrenal to spleen ratio (old formula) less than or equal to 0.72 indicate adenoma.

On the other hand, using new formula of adrenal to spleen ratio %, all adrenal adenomas had ratio of –30.68% or less, whereas all the non-adenomatous lesions ratio of –24.29% or more. If the value for the adrenal to spleen ratio% with new formula was taken from this range (–30.68 to –24.29%), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was 100%, and the cutoff value calculated from the ROC curve indicate that any adrenal lesion with adrenal to spleen ratio% (new formula) less than or equal to –27.82% indicate adenoma.

Using adrenal to liver ratio% we found all adrenal adenomas had ratio of –4.65% or less, all the non-adenomatous lesions ratio of –8.7% or more. If the value for the adrenal to liver ratio% was taken from this range (–8.7 to –4.65%), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was

92.3%, and the cutoff value calculated from the ROC curve indicate that any adrenal lesion with adrenal to liver ratio% less than or equal to –20.005% indicate adenoma.

Finally, using adrenal to muscle ratio%, all adrenal adenomas had ratio of –4.50% or less, whereas all the non-adenomatous lesions ratio of –9.31% or more. If the value for the adrenal to muscle ratio% was taken from this range (–9.31 to –4.50%), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was 92.3%, and the cutoff value calculated from the ROC curve indicate that any adrenal lesion with adrenal to muscle ratio% less than or equal to –6.05% indicative for adenoma.

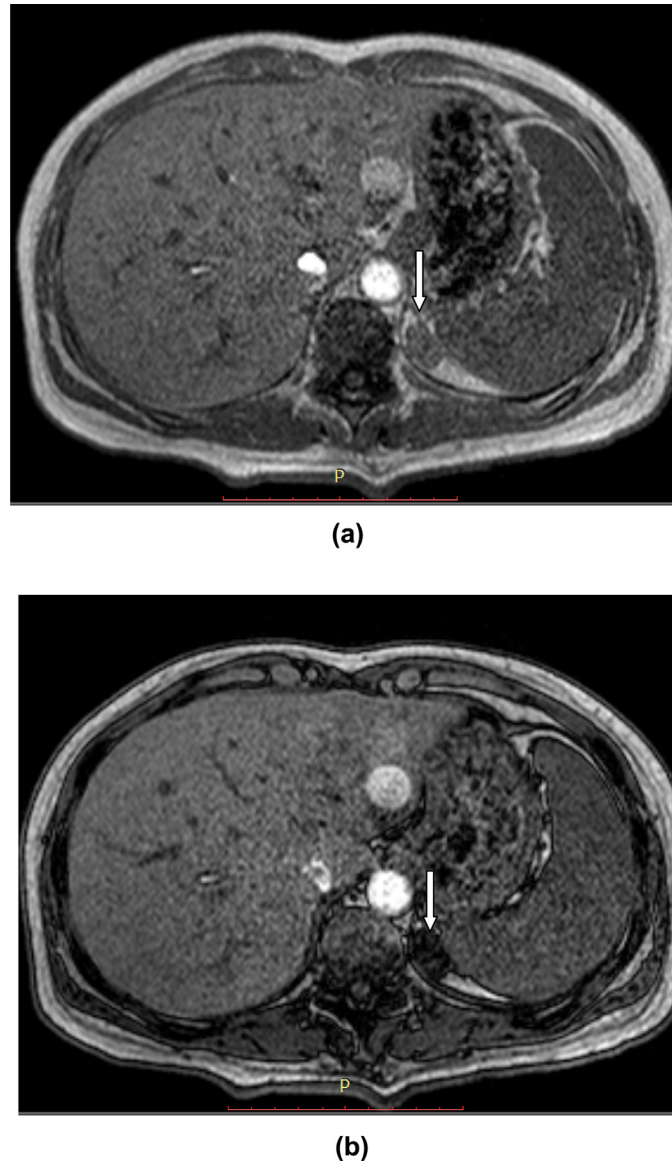
However, using ROC curve for chemical shift subtraction signal intensities it expressed significant difference between adenomas and non-adenomatous adrenal lesions with excellent area under the ROC curve ( $Az = 0.838$ ) and favorable sensitivity and specificity characteristics, with the ( $p < 0.000$ ) and suggested cutoff value of the signal intensity selected was 173.0475, as we found all adrenal adenomas had ratio of 108.87 or more, whereas all the non-adenomatous lesions ratio of 47.74 or less. If the value for the chemical shift subtraction was taken from this range (47.74–108.87), the accuracy for differentiating adenomas from non-adenomatous adrenal solid lesions was 80.8%.

## 5. Discussion

Characterizing nature of indeterminate adrenal mass with MRI updates was crucial along last years as imaging features for many lesions were not characterizing. As most adrenal adenomas contain intra-cytoplasmic lipid, whereas most of other solid lesions (notably malignant ones) contain no fat, so idea of differentiating benign adenomas from other solid adrenal tumors using chemical shift MRI imaging could limit the considerable imaging overlap guiding for the proper decision of management. Special situation of confusion faced if patient with known primary malignant lesion where differentiating adrenal adenomas from metastasis is a must [20].

Qualitative and quantitative studies using chemical shift methods to assess presence of fat in adrenal lesions through in-and opposed phase MRI sequences based on visual comparison of the signal drop between in- and opposed-phase images whereas quantitative method compared with adjacent structures in same section as a visual reference (as example with spleen, liver and muscles) [21].





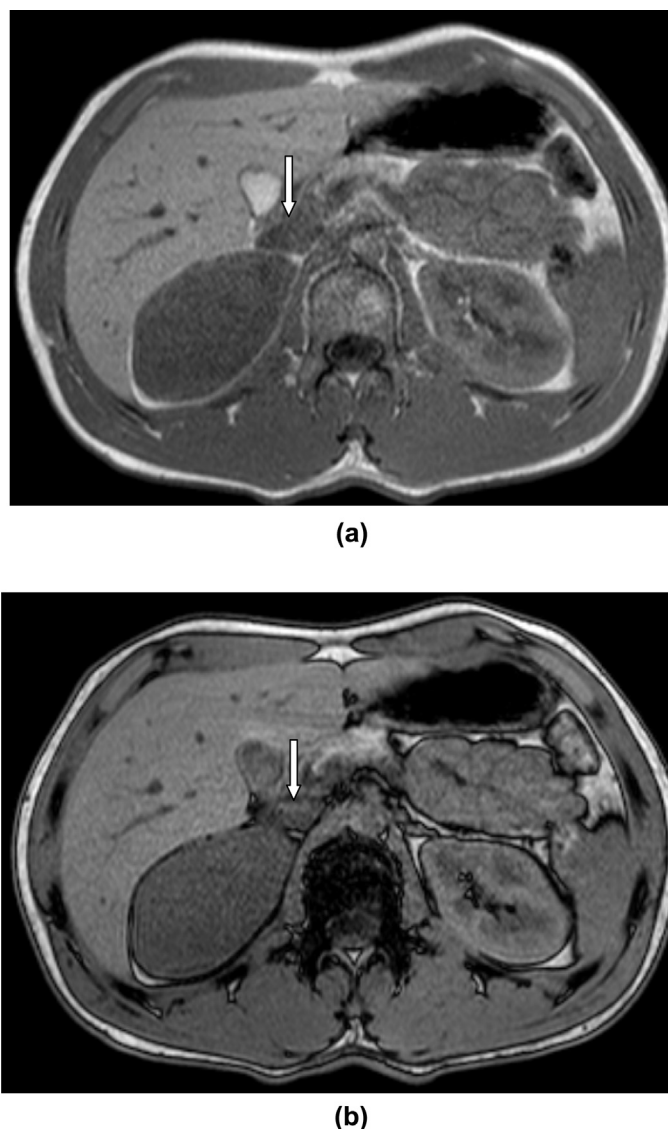
**Fig. 3.** 31-years female with both laboratory and post excision biopsy proved left adrenal aldosterone-producing adrenocortical adenoma. A, Axial in-phase MR image shows left adrenal mass (arrow) slightly isointense signals to spleen and paraspinal muscle. B, Axial opposed-phase MR image shows lower signal intensity of mass (arrow) compared to spleen and compared to its signal on A. Signal intensity index was 30.5%, adrenal to spleen ratio was 0.69, adrenal to spleen ratio% was –30.68%, adrenal to liver ratio% was –31.61% and adrenal to muscle ratio% was –31.5%.

Bilbey et al. [13] and Mayo-smith et al. [12] in previous studies assumed that adrenal-to-spleen ratio is the best quantitative chemical shift parameter in such discrimination and found no overlap in the results between adenomas and non-adenomas when the spleen was used as a reference organ rather than liver and paraspinal muscles (which showed some overlap in their results that was attributed to fatty infiltration of liver and adipose tissue in para-spinal muscles that altered the result during calculating the ratio of signal drop in opposed phase).

In the current study, the signal intensity index and adrenal-to-spleen ratio using either old or new formula considered the preferred parameters used in discrimination based on their better Az values seen on ROC analysis (1.000) however all other applied quantitative chemical shift parameters showed significant difference between adenomatous and non-adenomatous lesions ( $p < 0.001$ ).

McNicholas et al. [22] stated an algorithmic approach to adrenal masses based on their density in non-contrast CT and correlate it with MRI chemical shift adrenal to spleen ratio (ASR) and suggested that ASR less than 0.7 is indicative of benign adrenal lesion with no need for further work up were ASR more than 0.7 is probably malignant and biopsy is recommended for definite diagnosis.

In the current results, we much agreed with their results as when using old formula of adrenal to spleen ratio, all adrenal adenomas had ratio of 0.69 or less, while all non-adenomatous lesions had ratio of 0.72 or more with suggested cutoff value less than or equal to 0.72 indicative for adenoma. On the other hand when applying the new formula, we found all adrenal adenomas had ratio of –30.68% or less, whereas all the non-adenomatous lesions had ratio of –24.29% or more with the suggested cutoff value less than or equal to –27.82% indicated adenoma.



**Fig. 4.** 21-years male with biopsy proven right adrenal ganglioneuroma A, Axial in-phase MR image shows right adrenal mass (arrow) that slightly isointense in signal to spleen and paraspinal muscle. B, Axial opposed-phase MR image shows no significant drop of signal noted in the right adrenal mass (arrow) compared to its signal on A. Signal intensity index was 1.6%, adrenal to spleen ratio was 0.98, adrenal to spleen ratio% was –2%, adrenal to liver ratio% was 16.63% and adrenal to muscle ratio% was –4.21%.

Poor differentiation between adenomas and non-adenomatous lesions on using previous chemical shift imaging depending only on their signal intensity likely attributed to dispersion of lipid content in adenomas and small amount of lipid content found in non-adenomatous tumors as reported by Mitchell et al. [23] and Reinig et al. [24] showing that using signal intensity index is less reliable than other ratios.

Tsushima et al. [25] stated that signal intensity index for adenoma were significantly higher than other non-adenomas (metastasis and pheochromocytoma) with no overlap and reported that adenomas had SI indexes of more than 5%, while all metastatic tumors and pheochromocytomas had SI indexes of less than 5%.

Fujiyoshi et al. [20] and Barzilay and Pazianos [26] stated that the signal intensity index showed the greatest Az value of all quantitative chemical shift parameters eliminating the problem of signal intensity variability produced by using reference tissues with other parameters with an 100% accuracy when the cutoff value was 11.2–16.5%.

Sandrasegaran et al. [16] proved that figure of 23% is better than 16.5% as a cutoff value of signal intensity index. Al-Hawary et al.

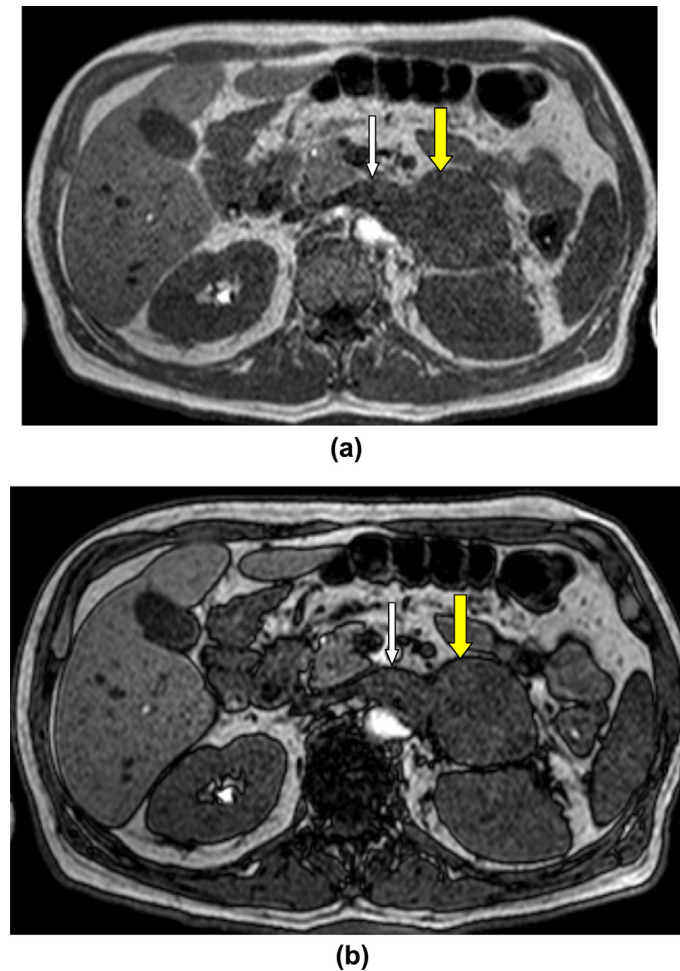
[15] stated that the signal intensity index measurement of any lesion is depending basically on the parameters used in chemical shift imaging as increasing T1 weighting by increasing the flip angle could result in overestimation of the fat content of the lesion.

In the current study, signal intensity index showed an equal accuracy for adrenal-to-spleen ratio with both Az areas being (1.000) and accuracy for differentiating adenomas from non-adenomatous solid lesions was 100%, and the cutoff value of signal intensity index greater than or equal to 23.4% indicate adenoma.

Although the signal intensity indexes for all adrenal adenomas were dispersed in our study, still they were all in the positive range with the lowest SI index 23.4% this is compatible to which stated by Tsushima et al. [25] as some adenomas had signal intensity indexes less than 10% and also matched with that stated by Fujiyoshi et al. [20] who mentioned lowest signal intensity index for adrenal adenoma was 16.5%.

Tsushima et al., also stated that the mean signal intensity indexes for adenomas and metastatic tumors were  $17.0 \pm 8.2\%$  and  $-6.8 \pm 9.2\%$ , respectively and Fujiyoshi et al., stated that the





**Fig. 5.** 54-years male with biopsy proven left adrenal carcinoma. A Axial in-phase MR image shows left adrenal mass (yellow arrow) that expresses isointense signal to spleen and paraspinal muscle with tumor thrombus seen extending into the left renal vein (white thin arrow) crossing the midline and not reaching the IVC. B, Axial opposed-phase MR image shows no significant drop of signal noted in the left adrenal mass (yellow arrow) nor in tumor thrombus (white thin arrow) compared to its signal on A. Signal intensity index was 6.3%, adrenal to spleen ratio was 0.98, adrenal to spleen ratio% was  $-1.92\%$ , adrenal to liver ratio% was  $-8.4\%$  and adrenal to muscle ratio% was  $22.2\%$ .

mean signal intensity indexes for adenomas and metastatic tumors were  $57.49 \pm 15.33\%$  and  $0.22 \pm 6.88\%$ , respectively. In the current study, we found the mean signal intensity indexes for adrenal adenomas and non-adenomatous lesions included metastasis were  $54.52 \pm 14.16\%$  and  $6.65 \pm 5.56$  respectively with mean signal intensity index of  $0.74 \pm 0.35$ .

Image subtraction as a post processing technique in evaluating efficacy of chemical shift MRI and characterizing adrenal masses have been reported by Savci et al. [27] and Korivi and Elsayes [28] when they subtracted opposed-phase images from in-phase images in an attempt to maximize the recognition of lipid content in adrenal lesions using double-echo chemical shift FLASH imaging sequence with single breath-hold with the corresponding in-phase and opposed-phase images obtained from identical anatomic position to avoid slice mis-registration followed by measuring signal intensity of adrenal masses in subtracted images.

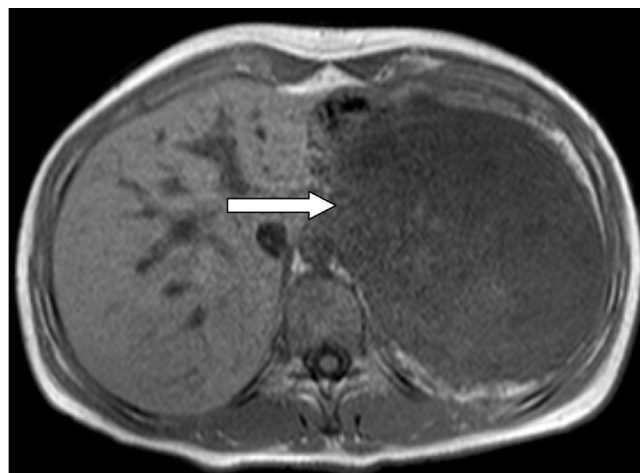
Savci et al., stated that there was a statistically significant difference in signal intensity values of adenomas and metastases (mean values, 213 versus 18), and differentiation of both lesions were 100% accurate if the cutoff value of the signal intensity selected was 36–106 with no need for reference tissue in measurement.

Our study stated that chemical shift subtraction MRI can provides highly confident differentiation of adrenal adenomas from non-adenomatous lesions just by measuring the signal intensity

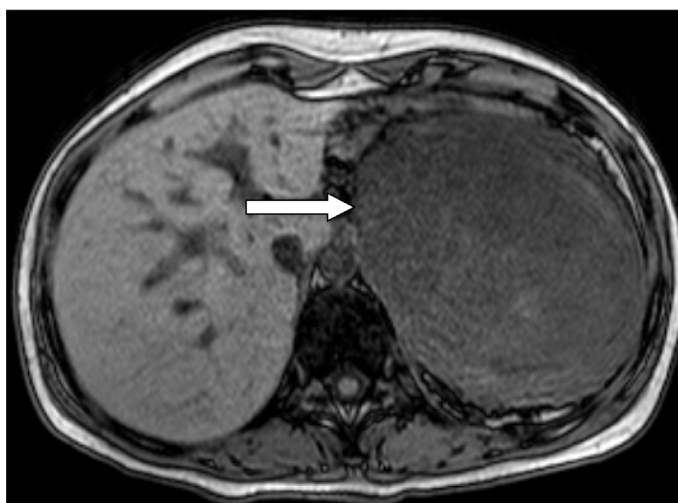
of the lesion only in the subtracted chemical shift image without using of any reference organ and without calculation of any formula with the cutoff of signal intensity 47–108, so any lesion with signal intensity more than 108 is indicating adenoma while any lesion less than 47 indicate non adenoma

We faced some limitation during current study while applying subtraction technique including first, the small number of adrenal lesions especially the functioning adenomas, non-adenomatous and metastatic adrenal lesion, second, all included studies were done using one MR scanner which may revealed other variable results if done using different scanners or other versions and lastly that no equivocal lesion was present among our cases such as lipid-poor adenomas.

In conclusion, the chemical shift MR imaging is being established as an important sequence that can give much help in diagnosing adrenal tumors, still some debate among various studies had been found in order to select the best chemical shift technique for evaluating adrenal lesions. In our study, the signal intensity index and adrenal-to-spleen ratios with the two used formulae, were the most reliable evaluation methods with no overlap found between adrenal adenomas and non-adenomatous solid tumors. Chemical shift subtraction MRI can also provide highly confident differentiation just by measuring the signal intensity of the lesion only in the subtracted chemical shift image without using of any reference organ.



(a)



(b)

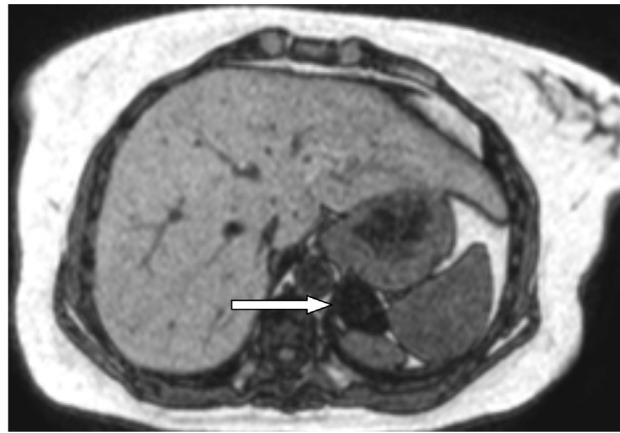


(c)

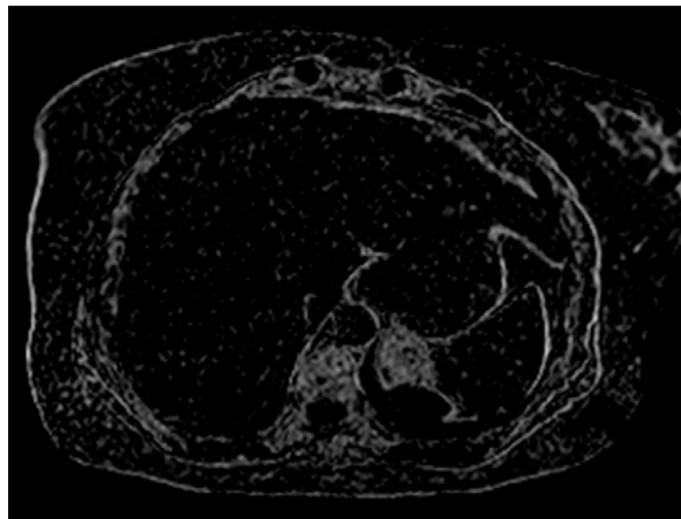
**Fig. 6.** 32-years female with biopsy proven left adrenal sarcoma. A, Axial in-phase MR image shows left adrenal mass (arrow) that slightly inhomogeneous iso to slight hypointense in signal compared to paraspinal muscle. B, Signal cancellation of mass (arrow) on opposed-phase MR image is obscure compared with that seen on A. Signal intensity index was 3.5%, adrenal to spleen ratio was 0.97, adrenal to spleen ratio% was  $-3.1\%$ , adrenal to liver ratio% was  $-1.14\%$  and adrenal to muscle ratio% was  $-3.11\%$ . C, T2-weighted MR image shows heterogeneous hyperintense signal of the left adrenal mass with central breakdown necrotic area.



(a)

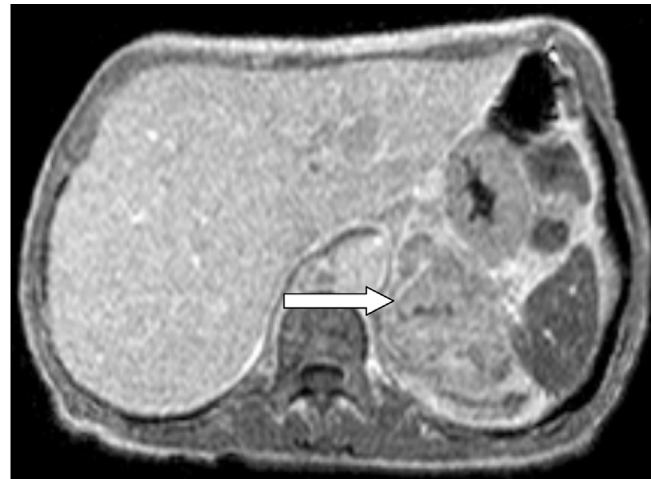


(b)

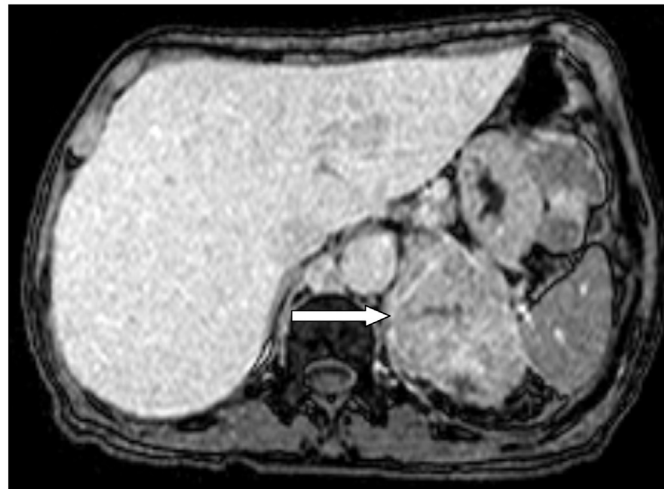


(c)

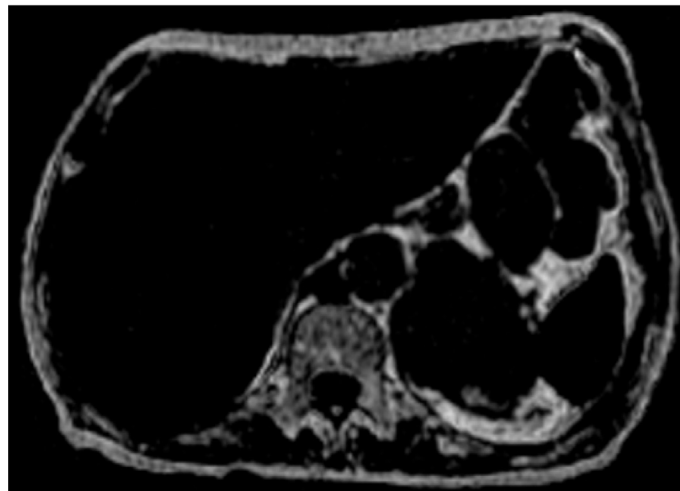
**Fig. 7.** 41-year female with laboratory and biopsy proven non-functional adenoma in left adrenal gland. A, Axial in-phase MR image shows left adrenal mass (arrow) that slightly iso- to slight hyper intense in signal compared to spleen. B, Axial opposed-phase MR image shows lower signal intensity of mass (arrow) compared to spleen and compared to its signal on A. Signal intensity index was 71.2%, adrenal to spleen ratio was 0.30, adrenal to spleen ratio% was –69.89%, adrenal to liver ratio% was –63.62% and adrenal to muscle ratio% was –69.85%. C, Chemical shift subtraction MR image shows marked signal increase throughout mass with signal intensity averaging 488.98, indicating lipid content.



(a)



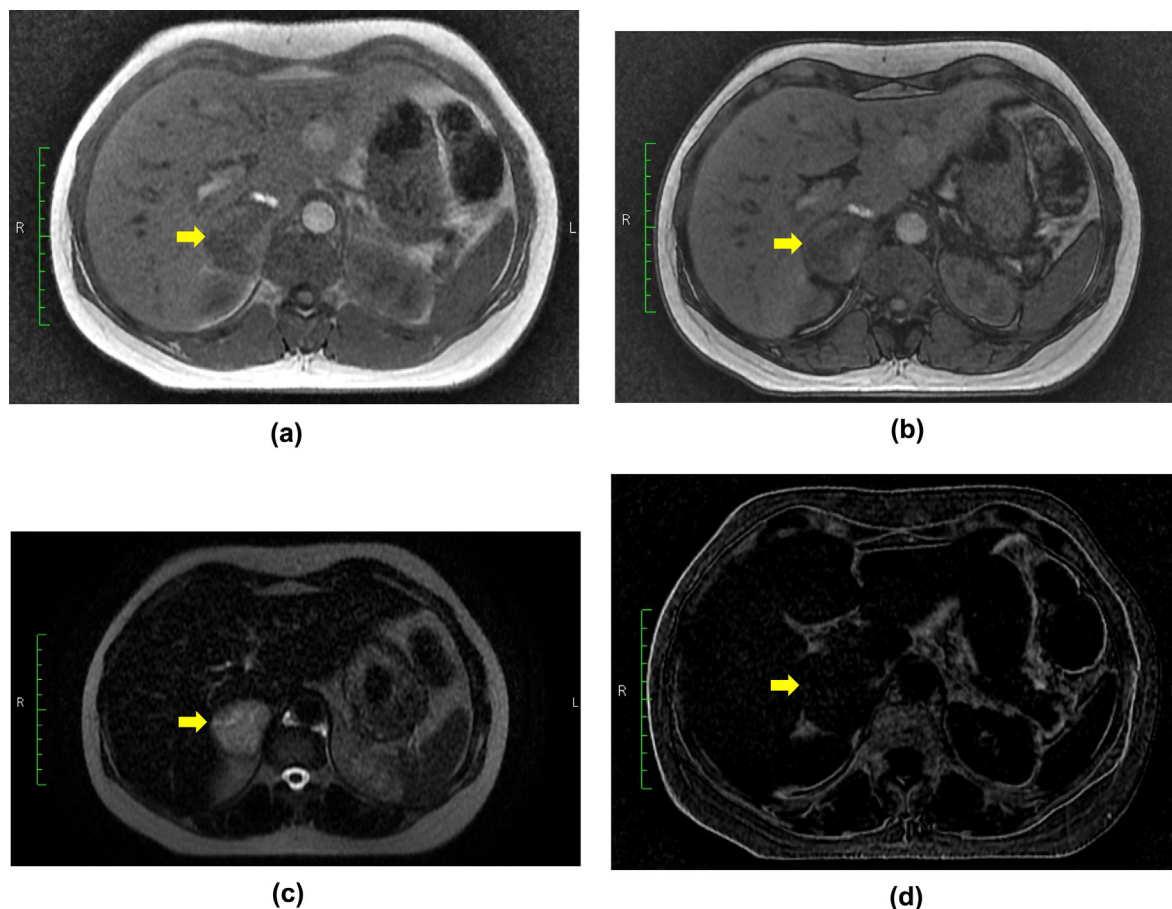
(b)



(c)

**Fig. 8.** 54-year male with left adrenal metastasis from lung cancer managed with chemotherapy. A, Axial in-phase MR image shows left adrenal mass (arrow) that hyper intense in signal compared to spleen. B, Signal cancellation of mass (arrow) on opposed-phase MR image is obscure compared with that seen on A. Signal intensity index was 1.1%, adrenal to spleen ratio was 0.80, adrenal to spleen ratio% was  $-19.71\%$ , adrenal to liver ratio% was  $-7.11\%$  and adrenal to muscle ratio% was  $7.55\%$ . C, Chemical shift subtraction MR image shows decreased signal throughout mass (arrow) with signal intensity averaging 13.52, indicating lipid content.





**Fig. 9.** 29-year female with repeated attacks of paroxysmal hypertension, the excisional biopsy revealed right suprarenal pheochromocytoma. A, Axial in-phase MR image shows right adrenal mass (yellow arrow) that expressed iso to slight hyperintense signal compared to spleen. B, Axial opposed-phase MR image shows no significant drop of signal noted in the right adrenal mass lesion (yellow arrow) with its signal intensity index was 5%, adrenal to spleen ratio was 0.97, adrenal to spleen ratio  $-3.19\%$ , adrenal to liver ratio was  $6.36\%$  and adrenal to muscle ratio was  $-9.31\%$ . C, Heavy T2-weighted image shows hyperintense signal of the right adrenal mass lesion (yellow arrow) (light bulb sign). D, Chemical shift subtraction MR image shows decreased signal of the right adrenal mass (yellow arrow) with signal intensity averaging 4.169, indicating absence of lipid content within the right adrenal mass lesion.

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